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APPLICATIONS OF OPTIMAL CONTROL THEORY TO IMMUNOLOGY

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Abstract - When an animal is challenged by a foreign substance which promotes an immune response, certain cells within the animal begin dividing, secreting antibody molecules, and differentiating into more specialized cell types. Optimal control theory is applied to ascertain the best strategy available to the immune system in allocating its cells. By examining a variety of mathematical models for cell populations and their antibody production, it is found that the optimal strategy of bang-bang control is robust. Experimental evidence which supports such strategies is also discussed.

I. INTRODUCTION

All vertebrates contain a collection of molecules and cells, called the immune system, designed to defend the animal from disease causing agents. When an animal is exposed to a foreign substance, an *antigen*, in the immunologists's jargon, a class of white blood cells, B lymphocytes, are stimulated to proliferate and secrete *antibody* molecules. Antibodies specifically bind to the antigen and lead to its elimination from the animal. Some B lymphocytes undergo further differentiation into plasma cells or memory cells. Plasma cells have lost their ability to divide and have specialized in secreting antibody at extremely high rates. Memory cells are resting (non-dividing) cells which do not secrete antibody, but rather remain in reserve for future encounters with antigen. Memory cells are believed to be responsible for our not getting many diseases a second time and their formation is the goal of preventive immunization programs.

In this paper I will show how optimal control theory can be applied to the study of B cell proliferation and differentiation. The work I will summarize has been done by me in collaboration with Majdedin Mirmirani and George Oster of the University of California, Berkeley.

Before beginning the mathematical discussion it is worthwhile to point out the philosophy underlying our calculations. One has to realize that there is no *a priori* reason why the immune system or any other biological system should beheve in an optimal fashion. Indeed, there is a very substantive question as to whether the notion of optimality can be given an operational meaning for many biological systems. Typically an organism must cope with many competing influ-

ences so that an improvement in one direction may involve a sacrifice in another. Thus optimality may have to be interpreted as a best compromise (e.g., Pareto) solution. Models of biological systems have now been developed which exhibit chaotic dynamics ±11. For such systems one is hard-pressed to say what is being optimized. Oster and others have shown that for certain systems, when the genetic constraints of Mendelian inheritance are imposed upon a population, it may become impossible for the population to optimize genetically controlled characteristics ±21. Even though one tends to think of evolution as an optimizing process, evolution is an historical process so that improvements generally proceed by small modifications of existing mechanisms. For such processes there exists ample opportunity to become trapped at local maxima. Further, even if a system is improving, it may not yet have had sufficient time to reach its optimum. In spite of all these difficulties many real biological systems, when examined closely, appear to perform a variety of tasks in an optimal fashion. The immune system which has been evolutionarily static for many tens of millions of years and is subject to extreme selection pressures seems a likely candidate for optimization by natural selection. Oster in his contribution to these proceedings will discuss other biological systems for which optimization arguments appear to be relevant.

II. OPTIMAL STRATEGY FOR PLASMA CELL FORMATION

A class of antigens, known as thymus-independent antigens, does not elicit the formation of memory cells. I will first examine the response to such antigens. Consider an experimental animal given a single injection of a non-proliferating thymus-independent antigen such as a bacterial coat polysaccharide. This antigen stimulates the formation of a population of large lymphocytes, L, which can either proliferate with constant per capita birth rate b or differentiate into plasma cells with constant per capita differentiation rate d (see Fig. 1). Lymphocytes and plasma cells have finite lifetimes and die at per capita rates μ_L and μ_p, respectively. I assume $b > \mu_L$ so lymphocytes grow at a positive net rate. On the time scale of an immune response the death of large lymphocytes is usually negligible, while the death of plasma cells can be substantial. Large lymphocytes each secrete antibody, A, at a modest rate $k > 0$, while plasma cells each are assumed to secrete antibody at a substantially higher rate γk, $\gamma > 1$. Determinations of the rate of protein synthesis of these two cell types indicate that γ can be as large as 1000, although values between 10 and 100 might be more typical. At any time $t \geq 0$ I assume that a fraction of the lymphocytes, $u(t)$, $0 \leq u(t) \leq 1$, are proliferating while the remaining fraction, $1 - u(t)$, are differentiating into plasma cells. The problem I wish to consider is how should an animal apportion its stimulated cells between lymphocytes and plasma cells, so as to secrete an amount of antibody A^* sufficient to neutralize the antigen in minimal time,

Figure 1

Stated formally we have the following bilinear optimal control problem

$$\min_{u(\cdot)} J = \int_0^T dt \tag{1}$$

subject to the dynamic constraints

$$\dot{A} = k(L + \gamma P) \tag{2}$$

$$\dot{L} = bu(t)L - d[1 - u(t)]L - \mu_L L \tag{3}$$

$$\dot{P} = d[1 - u(t)]L - \mu_P P \tag{4}$$

and the static constraint

$$0 \leq u(t) \leq 1 \tag{5}$$

where the control $u(\cdot)$ is a bounded, measureable, real valued function. As an initial manifold I wish to consider only the point

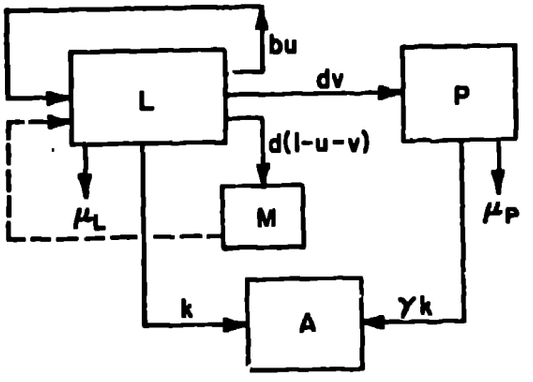
$$A(0) = 0 \tag{6}$$

$$L(0) = L_0 > 1 \tag{7}$$

$$P(0) = 0 \tag{8}$$

while the terminal manifold is given by

$$A(t) - A^* = 0 \tag{9}$$


bu
L
dv
P
d(1-u-v)
μ_L
M
μ_P
k
A
γk

Geometrically, the problem I am considering is to find the function $u(\cdot)$ which yields a trajectory minimizing the transit time between the initial and final manifolds.

Optimal control problems of this type can be solved by Pontryagin's maximum principle. Introducing a set of adjoint variables $\{\lambda_0,\lambda_1,\lambda_2,\lambda_3\}$ the Hamiltonian is seen to be

$$H = \lambda_0 + \lambda_1[k(L + \gamma P)] + \lambda_2[bu - d(1-u) - \mu_L]L + \lambda_3[d(1-u)L - \mu_P P]$$

$$= L[(b+d)\lambda_2 - d\lambda_3]u + \text{terms not involving } u \tag{10}$$

The extremal control u^* is obtained by maximixing H. Thus

$$u^*(t) = \begin{cases} 1 & \text{if } \sigma(t) > 0 \\ \in[0,1] & \text{if } \sigma(t) = 0 \text{ on a non-zero time interval} \\ 0 & \text{if } \sigma(t) < 0 \end{cases} \tag{11}$$

where

$$\sigma(t) \triangleq (b+d)\lambda_2(t) - d\lambda_3(t) \tag{12}$$

is the switching function.

The adjoint equations are

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial A} = 0 \tag{13}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial L} = -k\lambda_1 - [bu - d(1-u) - \mu_L]\lambda_2 - d(1-u)\lambda_3 \tag{14}$$

$$\dot{\lambda}_3 = -\frac{\partial H}{\partial P} = -\gamma k\lambda_1 + \mu_P\lambda_3 \tag{15}$$

with boundary conditions

$$\lambda_1(T) = 1, \qquad \lambda_2(T) = \lambda_3(T) = 0 \tag{16}$$

Using the adjoint equations one can easily exclude the possibility of $\sigma(t)$ being zero on a non-zero time interval (a singular arc) [3]. Thus the control is bang-bang and only takes on the values 0 and 1. The remaining analysis of the switching function reduces to two cases. If $\dot{\sigma}(T) = k[d(\gamma-1) - b] < 0$ then one can show by directly integrating the adjoint equations backwards in time that $u^*(t) = 1$, $t \in [0,T]$. Alternatively, if $\dot{\sigma}(T) > 0$ then either $u^*(t) = 0$, $t \in [0,T]$ or there is a single switch, i.e.,

$$u^*(t) = \begin{cases} 1 & 0 \leq t < t^* \\ 0 & t^* < t \leq T \end{cases} \tag{17}$$

When a switch occurs, the optimal final time T^*, and the switching time t^* are given by

$$t^* = \frac{1}{b_L} \ln \frac{A^* b_L + kL_0}{b_L kL_0 G(\tau^*)} \tag{18}$$

$$T^* = t^* + \tau^* \tag{19}$$

where

$$G(\tau^*) \triangleq \frac{1}{b_L} + \frac{\mu_P + \gamma d}{\mu_{Ld}\mu_P} - \left(\frac{\mu_P - \mu_{Ld} + \gamma d}{\mu_{Ld}(\mu_P - \mu_{Ld})}\right) \exp(-\mu_{Ld}\tau^*) + \frac{\gamma d}{\mu_P(\mu_P - \mu_{Ld})} \exp(-\mu_P \tau^*) \tag{20}$$

$b_L \triangleq b - \mu_L$, $\mu_{Ld} \triangleq \mu_L + d$, and τ^* is the solution to

$$\sigma(\tau^*) = B \exp(-\mu_P \tau^*) + C \exp(-\mu_{Ld}\tau^*) + D = 0 \tag{21}$$

Here

$$B = \frac{d\gamma k}{\mu_P}\left[1 + \frac{b + d}{\mu_P - \mu_{Ld}}\right] \tag{22}$$

$$C = \frac{(b+d)k}{\mu_P}\left[\frac{\mu_P + \gamma d}{\mu_{Ld}} + \frac{\gamma d}{\mu_P - \mu_{Ld}}\right] \tag{23}$$

$$D = \frac{k}{\mu_{Ld}}\left[b+d + \frac{\gamma d b_L}{\mu_P}\right] \tag{24}$$

and 1 have assumed $\mu_P \neq \mu_{Ld}$ as is the case when typical biological parameter values are employed.

In order to determine if a switch in fact occurs one integrates the state equations, (2)-(4), with $u = 0$ and determines the time $\bar{t}$ at which the final manifold is obtained, $A(\bar{t}) = A^*$. If $\bar{t} < \tau^*$ the extremal strategy is $u^*(t) = 0$, $t \in [0, T^*]$, and $T^* = \bar{t}$. On the other hand if $\bar{t} > \tau^*$ then a switch occurs. For the parameter set $b = d = 0.1$ hr, $\mu_P = 0.2$ hr^{-1}, $\mu_L = 10^{-5}$ hr^{-1}, and $\gamma = 10$, one finds $\tau^* = 12.2$ hr. Additionally, if $\alpha \triangleq A^*/kL_0 < 50$ hr then no switch occurs. However, a typical value for α is 2×10^5 hr [2] and thus a single switch is to be expected.

By establishing a correspondence between the free end time problem considered above and the problem of maximizing the antibody production over a fixed time one can show that Leitman and Stalford's [4] sufficiency conditions for an optimal control are satisfied [3]. Thus u*, as calculated above, is not only an extremal control, but also an optimal control.

A series of more complicated but biologically more realistic models has also been examined. One can directly include antigen and minimize the time to bring the antigen concentration down to a safe level. The extremal control is again bang-bang when $d(\gamma-1) - b \leq 0$, and I expect, although I have not proven, that there is at most one switch. The biologically irrelevant case (see below), $d(\gamma-1) - b \leq 0$, has not been examined. One can also include other known biological features in the model: a source for additional stimulated lymphocytes, time delays, or a time dependent rate of antibody secretion, k(t). In all of these instances one finds that bang-bang control is again extremal and that at most one switch occurs. Consequently, one is led to believe that the predictions of the preceeding simple model are robust and may have biological significance.

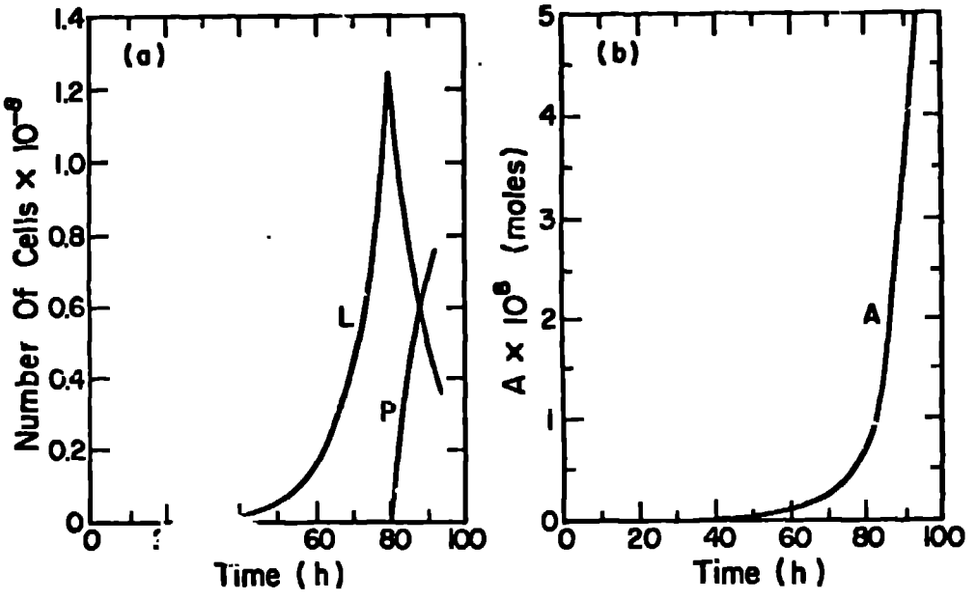
III. BIOLOGICAL DISCUSSION OF RESPONSE TO THYMUS INDEPENDENT ANTIGENS

The optimal strategy for producing an amount of antibody A* sufficient to neutralize a given antigenic assault in the shortest time is found to be: (a) if $(\gamma-1)d \leq b$, $u^*(t) = 1$, $0 \leq t \leq T^*$ i.e., produce only large lymphocytes. Realistic parameter values are $d \approx b$ and $\gamma > 10$, so this case should not be relevant to the biological situation; (b) if $(\gamma-1)d > b$ then it is advantageous to convert lymphocytes into plasma cells. The time at which this differentiation should proceed depends on the antigen concentration, or in this simple model A*. If A* is sufficiently small then the optimal strategy is $u^*(t) = 0$, $0 \leq t \leq T^*$, i.e., immediately differentiate into plasma cells without proliferating. Clearly this strategy is viable only if plasma cells during their finite lifetimes can produce an amount of antibody A*, otherwise proliferation is necessary. Thus if A* is larger than a critical amount the optimal strategy is $u^*(t) = 1$, $0 \leq t < t^*$, $u^*(t) = 0$, $t^* < t \leq T^*$, i.e., proliferate first and then switch to plasma cell production. Examining antigen doses that experimentally are required to stimulate noticeable immune responses one finds that A* is typically orders of magnitude greater than the critical value require to give a switch. Thus the major prediction of this optimal control model is that following a single injection of a thymus independent antigen there first should be lymphocyte proliferation followed late in the immune response by plasma cell production. Using realistic biological parameter values, say $b = d = 0.1$ hr, $\mu_p = 0.2$ hr^{-1}, $\mu_L \leq 10^{-3}$ hr^{-1}, $10 \leq \gamma \leq 100$, and $\alpha = 2 \times 10^5$ hr, the switching times are found to

roughly lie between 55 and 80 hr [3]. The computed dynamics of an immune response following the optimal strategy is illustrated in Fig. 2. Sensitivity studies show that in the range of realistic parameter values these curves are very representative of the optimal response dynamics.

The biological evidence supporting the optimal strategy is of two types: kinetic and morphological. Since plasma cells secrete antibody much more rapidly than large lymphocytes one can experimentally attempt to determine the secretion rates of the various cells participating in an immune response as a function of time after antigen injection. Experiments of this type by Baker et al [5,6] showed that in the response to type III pneumococcal polysaccharide, an antigen that does not produce any detectable memory [5], two types of antibody-producing cells are formed, antigen reactive cells (ARC) which secrete antibody slowly and arise at an exponential rate and plaque forming cells (PFC) which secrete antibody rapidly. With an optimal immunizing dose of SSS-III, maximal numbers of ARC are seen 2 days after immunization. At about this same time serum antibody is detected and PFC begin to appear. If one identifies the slow secreters (ARC) with large lymphocytes and the rapid secreters (PFC) with plasma cells then the observation of Baker et al is in accordance with the predictions of the optimal control model (see Fig. 2).

Morphological studies can also be combined with kinetic studies to determine when, in the immune response, plasma cells are formed. Such studies are clearly more tedious to perform since large numbers of cells must be scanned to extract a subpopulation which is secreting antibody and these cells must then be examined microscopically. Russell and Diener [7] studied the early phase of the primary


(a)
Number Of Cells x 10^{-8}
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
L
P
0
60
80
100
Time (h)
(b)
A x 10^{8} (moles)
5
4
3
2
1
0
A
0
20
40
60
80
100
Time (h)

immune response to the thymus independent antigen polymerized flagellin prepared from the flagella of *Salmonella adelaide*. During the first four days of the *in vivo* response they noticed "a striking paucity of antibody-forming plasma cells." Similar morphological studies by Zagury et al [8] on the response to horseradish perioxidase in rabbits showed that the percentage of antibody-secreting lymphocytes was a maximum when antibody secreting activity was first detected (day 7) and then declined, while the percentage of plasma cells increased with time, reaching a maximum late in the response (day 18).

The biological evidence confirms the qualitative predictions of the optimal control model. As of yet no quantitative comparisons have been made. However, for the sake of argument let us assume that the immune system does in fact regulate its cell populations in a bang-bang fashion. One must then ask how does the immune system decide when to switch? For thymus-dependent antigens, substantial evidence has now been accumulated showing that antigen alone is sufficient to cause B cell proliferation, but that another lymphocyte, type T cells, are required for the differentiation and maturation of the B cell [9-11]. T cells apparently control B cell differentiation by secretion of a soluble factor, but the mechanisms regulating the release of this factor are unknown. In the response to thymus independent antigens, T cells are not required and other explanations must be sought. Studies of B cells in culture have indicated that high cell densities favor maturation to non-dividing plasma cells, while cultures of the same cells at low densities favor proliferation [12]. Further, the lower the initial cell density in a culture the longer the proliferative response and the later the peak in the plaque forming cell response [12]. (Plaque forming cells are cells which secrete sufficient amounts of antibody so as to be detectable by the hemolytic plaque assay.) These experiments argue for the presence of closed loop control in the B cell response. Models need to be formulated and analyzed, incorporating the dependence of B cell proliferation and differentiation on factors such as the antibody and antigen concentration, the fraction of cell receptor sites bound, or their rate of being occupied, and the cell density.

IV. OPTIMAL STRATEGY FOR MEMORY CELL FORMATION

The immune response to more than one encounter with the same antigen is usually characterized by a phenomenon called immunological memory, in which the second and subsequent challenges induce more rapid and more vigorous antibody responses than the first. Figure 3 illustrates the typical dynamics of the primary and secondary immune responses The memory of the first encounter with antigen is carried by cells which for obvious reasons have been termed memory cells. Although there is some question as to precisely which B cells become

Figure 3

memory cells, I shall adopt the model shown in Fig. 4 in which memory cells are generated from large lymphocytes. Memory cells are very long lived so no death rate for them has been incorporated into the model. Additionally, as shown ir the figure, memory cells are believed not to secrete antibody. Memory cells generated during a primary immune response, transform into large lymphocytes, on subsequent encounters with antigen, thus providing a greatly increased initial pool of cells responsive to previously fought antigens.

As depicted in Fig. 4 large lymphocytes now have three choices: they can remain proliferating cells and secrete modest amounts of antibody, differentiate into plasma cells and secrete large amounts of antibody but at the expense of being short-lived, or they can differentiate into non-antibody secreting memory cells and be held in reserve for later encounters with antigen. One can again ask how such a system should be controlled in order to provide optimal survival value to the organism. If one chooses the elimination of antigen in minimal time as an optimization criterion then in the response to a single challenge with antigen no memory cells should be formed. Instead, consider the more realistic situation in which antigen is encountered many times with probability p_i for the ith encounter. The appropriate optimization criterion would then seem to be

$$\min J = \sum_{i=1}^{\infty} p_i \int_0^{T_i} dt \qquad (25)$$

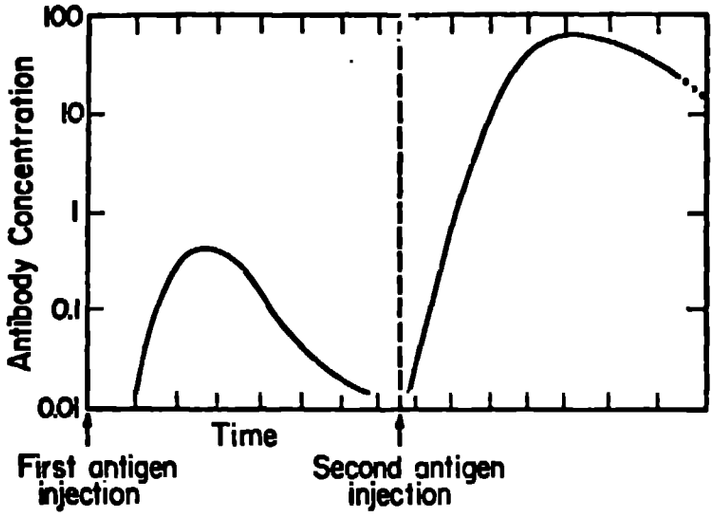

100
10
1
0.1
0.01
Antibody Concentration
Time
First antigen injection
Second antigen injection

Fig 3

where T_i is the time required to eliminate the antigen on the ith encounter. A more complete discussion of the appropriate choice for an optimization criterion can be found in [12].

In order to elucidate the optimal strategy for B memory cell production it suffices to consider 2 encounters with antigen, the first occurring with probability 1 and the second with probability p [12]. Thus the criterion (25) reduces to

$$\min_{u(\cdot),v(\cdot)} J = \int_0^{T_1} dt + p\int_0^{T_2} dt \tag{26}$$

where T_1 and T_2 are the times required to secrete amounts of antibody A_1^* and A_2^*, respectively, needed to neutralize the antigen in the primary and secondary responses. The dynamic constraints are simply generalizations of Eqs. (2)-(4) and, as can be seen from Fig. 4, are

$$\dot{A} = k(L + \gamma P) \tag{27}$$

$$\dot{L} = bu(t)L - dv(t)L - d[1 - u(t) - v(t)]L - \mu_L L \tag{28}$$

$$\dot{P} = dv(t)L - \mu_P P \tag{29}$$

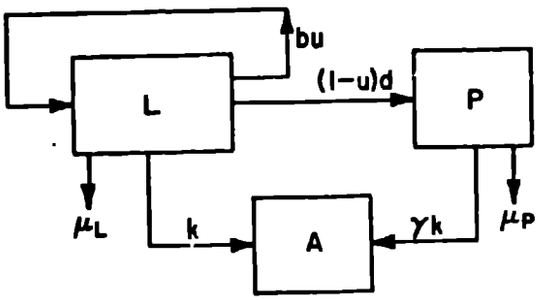


Fig 4

$$\dot{M} = d[1 - u(t) - v(t)]L \qquad (30)$$

The initial conditions for the primary response are

$$A(0) = P(0) = M(0) = 0 \quad \text{and} \quad L(0) = 0 \qquad (31)$$

whereas for the secondary response the initial conditions are

$$A(0) = P(0) = 0, \quad M(0) = M_{20} \quad \text{and} \quad L(0) = \Lambda M(T_1) + L_{20} \qquad (32)$$

Here I have assumed that the second encounter with antigen occurs sufficiently long after the first encounter that the primary response has ceased, all remaining plasma cells have died and all secreted antibody has been catabolized. The initial number of lymphocytes responding to the antigen is assumed to be a fraction $0 \leq \Lambda \leq 1$ of the memory cells left at the end of the primary response which have survived until the second infection, plus a small number, L_{20}, of lymphocytes which naturally become stimulated by the antigen. A number M_{20} os the surviving memory cells are not stimualted to become large lymphocytes and thus $M(0) = M_{20}$.

The calculation of the optimal response can be greatly simplified by observing that during the secondary response no memory cells should be produced since antigen is sure never to be seen again. Thus the secondary response should be carried out in the fashion computed in Section II. If we assume A_2^* is large, then there is a single switch during the secondary response and T_2^* is given by Eqs. (18) and (19) with L_0 replaced by $\Lambda M(T_1) + L_{20}$. Notice T_2^* is a function of $M(T_1)$ and thus the optimization problem

$$\min_{u(\cdot),v(\cdot)} J = \int_0^{T_1} dt + pT_2^* \qquad (33)$$

becomes a minimal time problem with terminal cost which can be solved by Pontryagin's principle [13].

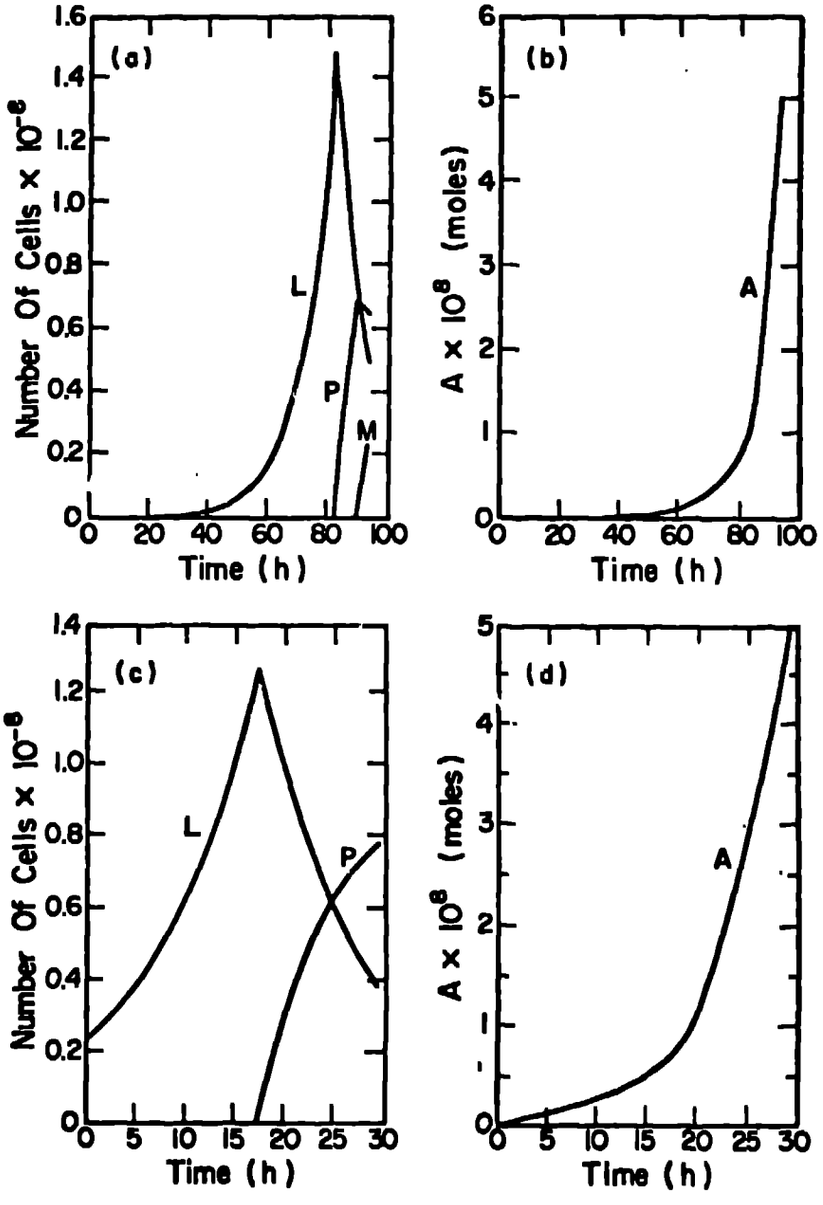
The extremal solution for the primary response, computed in ref. [12], is again bang-bang. However, now the sequence of switches depends crucially upon the parameter p. Let $\underset{\sim}{U}(t) = [u(t),v(t)]$ be the control vector. If A_1^*, the required antibody production, is larger than some critical value, then there are 3 possible switching sequences, with the initial phase always being lymphocyte proliferation, $\underset{\sim}{U} = (1,0)$. This is then followed by (A) a switch to plasma cell production, $\underset{\sim}{U} = (0,1)$, followed by a switch to memory cell formation, $\underset{\sim}{U} = (0,0)$, or (B) a switch to plasma cell formation, succeeded by a switch back to lymphocyte proliferation, and then a final switch to memory cell formation, or (C) a

switch to memory cell production. I will refer to these three possible strategies as (L,P,M), (L,P,L,M) and (L,M). If A_1^* is sufficiently small no initial phase of lymphocyte proliferation will be necessary and the additional strategies: (M), (P,M), and (P,L,M) may occur. One important conclusion is that in all cases memory cells are only produced at the end of the response. For the biologically interesting case of large A_1^* one finds that for small values of p, where the secondary response is not weighted very heavily, the extremal strategy is (L,P,M), i.e., proliferate first, then differentiate into plasma cells, and towards the end of the response make memory cells. For somewhat larger values of p the extremal strategy changes f.. more emphasis is placed on making memory cells. After plasma cells are formed the lymphocyte population is depleted and thus to make large numbers of memory cells the lymphocyte population must first expand. Thus the strategy becomes (L,P,L,M). For somewhat higher vlaues of p one finds the extremal strategy switches back to (L,P,M) with a lengthened initial lymphocyte proliferation phase. Finally, for very high values of p, the extremal strategy simply becomes (L,M). Here the number of memory cells is so large that in order to generate them one needs a lymphocyte population which in itself is sufficiently large that it can handle the primary infection.

IV. BIOLOGICAL DISCUSSION OF THE EXTREMAL STRATEGIES FOR MEMORY CELL FORMATION

The (L,M) strategy generally entails the production of an unrealistically large number of lymphocytes and memory cells. At such high population densities lymphocyte growth is probably logistic, not exponential, and hence I doubt if this strategy would commonly come into play in real biological systems. Further, if one examines the cost functional J for each of the strategies one finds that the (L,P,L,M) strategy provides a negligible advantage over the simplier (L,P,M) strategy. For reasons of economy, I expect that the (L,P,L,M) strategy would not be utilized and thus I predict that only the (L,P,M) strategy would be found in real biological systems.

The dynamics of the primary response using the (L,P,M) strategy and the subsequent secondary response using the optimal (L,P) strategy computed in Section II is illustrated in Fig. 5. Notice that the primary response takes nearly 100 hr while the secondary response takes only 30 hr. Also in the primary response the antibody concentration is nearly zero for the first 60 hr, whereas in the secondary response no measureable lag occurs in the production of antibodie.. These curves which illustrate the amount of antibody produced cannot be directly compared to those in Fig. 4, which show the actual serum antibody concentration and thus include the effects of the elimination of antibody by combination with antigen and natural metabolic breakdown. However, the curves do illustrate the


(a)
Number Of Cells x 10^{-8}
L
P
M
Time (h)
(b)
A x 10^{8} (moles)
A
Time (h)
(c)
Number Of Cells x 10^{-8}
L
P
Time (h)
(d)
A x 10^{8} (moles)
A
Time (h)

greater efficiency of the secondary response and the observed lack of a lag in antibody production.

The most significant prediction of the optimal control calculation is that memory cells should be produced at the end of a primary response. This, of course seems almost obvious. Since memory cells produce no antibody and hence provide no advantage to the current response they should only be formed once the current infection has been successfully handled.* Some but not all biological evidence supports this conclusion as detailed below:

1) The average affinity of antibody secreted during a secondary response is high and is about the same as the average affinity seen at the end of the primary response. This is consistent with the notion that lymphocytes secreting high affinity antibody at the end of the primary response become memory cells.

2) A variety of studies aimed at examining the kinetics of memory cell formation found that the major increase in the number of B memory cells occurs after the peak of antibody forming cells has been detected [14-15]. However, one study found that antibody forming cells and memory cells appeared simultaneously [16].

3) Memory cells are believed to be formed in the germinal centers of lymph nodes, which are structures whose formation is induced by antigen late in an immune response. Destruction of the germinal centers was found to leave the dynamics of antibody formation unaffected but to eliminate immunological memory [17,18]. Although other explanations are possible the most obvious is that germinal centers are required for the production of memory cells and that such generation takes place after the formation of plasma cells.

V. DIRECTION FOR FUTURE RESEARCH

The solutions to the optimal control problems that I have discussed appear to be consistent with biological reality. Besides leading one to believe that the immune system might in fact have been optimized by natural selection, the computations have shed some light on immunological control strategies. Given these initial successes it seems worthwhile to examine even more realistic models. The antigens dealt with so far have been non-replicating. However, the immune system has clearly been designed as a defense mechanism against growing antigens such as pathogenic organisms or tumor cells. The explicit inclusion of a growing antigen leads to nonlinear state space models of at least 4 dimensions. A simple

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* This line of reasoning leads one to believe that T_1, the time at which $A(T_1) = A_1^*$, may not be the appropriate time to terminate the primary response in so far as memory cell production is concerned. See ref. [12] for further discussion of this important modeling consideration.

model of this type that I am working on with Sol Rocklin of the University of California at Berkeley differs fundamentally from the models already presented in that singular control becomes possible and the state and adjoint equations become so intricately coupled that numerical solutions become necessary. An added complication that seems necessary is to use logistic rather than exponential growth equations for both the lymphocytes and antigen so as to avoid obtaining strategies such as (L,M) which generate unrealistically large cell populations. Of a more fundamental nature is the recognition that the models considered so far only deal with the immune response to a single antigen. However, in actuality an animal is constantly bombarded by a multitude of different antigens all of which must be coped with to ensure survival. Since the number of lymphocytes in an animal is maintained relatively constant, an organism by expanding the population of cells reactive to one antigen must be decreasing populations of cells with other antigen specificities. Such effects need to be considered and should lead to some very interesting stochastic allocation models.

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FIGURE CAPTIONS

Fig. 1. Block diagram of B cell proliferation and plasma cell formation.

Fig. 2. Optimal response dynamics. (a) the number of large lymphocytes and plasma cells as a function of time. (b) The amount of antibody secreted as a function of time with $b = d = 0.1\ hr^{-1}$, $\mu_P = 0.02\ hr^{-1}$, $\mu_L = 10^{-5}\ hr^{-1}$, $\gamma = 10$, $L_0 = 4 \times 10^4$, $k = 6 \times 10^{-8}$ moles $cell^{-1}\ hr^{-1}$ and $A^* = 5 \times 10^{-8}$ moles.

Fig. 3. The immune response to the same antigen given at two widely spaced times.

Fig. 4. Block diagram of B cell proliferation and differentiation into plasma cells and memory cells.

Fig. 5. Dynamics of the optimal primary and secondary responses with $p = 0.1$, $k = 6.25 \times 10^{-16}$ moles $cell^{-1}\ hr^{-1}$, $A_1^* = A_2^* = 5 \times 10^{-8}$ moles, $L_0 = 4 \times 10^4$, and $L_{20} = 4 \times 10^3$. (a) The number of large lymphocytes, plasma cells and memory cells produced as a function of time during the primary response. (b) The number of moles of antibodies secreted as a function of time during the primary response. (c) The number of large lymphocytes and plasma cells produced during the secondary response. (d) The antibody secretion during the secondary response.